EXHIBIT F

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Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)

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Abstract

Few studies have directly compared the clinical features of neuropathic and non-neuropathic pains. For this purpose, the French Neuropathic Pain Group developed a clinician-administered questionnaire named DN4 consisting of both sensory descriptors and signs related to bedside sensory examination. This questionnaire was used in a prospective study of 160 patients presenting with pain associated with a definite neurological or somatic lesion. The most common aetiologies of nervous lesions ($n=89$) were traumatic nerve injury, post herpetic neuralgia and post stroke pain. Non-neurological lesions ($n=71$) were represented by osteoarthritis, inflammatory arthropathies and mechanical low back pain. Each patient was seen independently by two experts in order to confirm the diagnosis of neuropathic or non-neuropathic pain. The prevalence of pain descriptors and sensory dysfunctions were systematically compared in the two groups of patients. The analysis of the psychometric properties of the DN4 questionnaire included: face validity, inter-rater reliability, factor analysis and logistic regression to identify the discriminant properties of items or combinations of items for the diagnosis of neuropathic pain. We found that a relatively small number of items are sufficient to discriminate neuropathic pain. The 10-item questionnaire developed in the present study constitutes a new diagnostic instrument, which might be helpful both in clinical research and daily practice.

Keywords: Neuropathic pain; Diagnostic tools; Clinical assessment; Psychometric validation; Questionnaire

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1. Introduction

According to the definition of the International Association for the Study of Pain (IASP) the term neuropathic pains refers to all *pains initiated or caused by a primary lesion or dysfunction of the nervous system.* Such a broad category includes highly heterogenous and difficult to treat clinical conditions associated with a large variety of peripheral or central nervous lesions. This definition of neuropathic pain has long been and remains a matter of controversy (e.g. Backonja, 2003; Bennett, 2003; Hansson, 2003; Max, 2002). Most of the discussion concerns the term 'dysfunction' which is considered too vague by many authors. Indeed, several conditions not associated with a clearly identified lesion such as fibromyalgia, irritable bowel syndrome, stomatodynia or migraine have sometimes been included in this category since they may involve a dysfunction of the nervous system. This definition issue raises the question of the diagnosis of neuropathic pain and, more generally, the relevance of the distinction of patients with a definite neurological lesion.

Clinically, neuropathic pain is generally characterized by the association of unspecified positive and negative sensory symptoms, but there are still no consensus diagnostic criteria of neuropathic pain (Dworkin et al., 2003; Hansson, 2002; Jensen et al., 2001; Woolf and Mannion, 1999). Surprisingly, few studies aimed to compare directly the characteristics of pain associated with a neurological lesion with those associated with other somatic lesions (Boureau et al., 1990; Masson et al., 1989; Bennett, 2001; Krause and Backonja, 2003). Most of these studies included patients without identified nerve lesion (e.g. Complex Regional Pain Syndrome (CRPS) type I), patients with pain presumably of mixed origin (e.g. lumboradicular, cervicobrachial) (Boureau et al., 1990; Bennett, 2001) or did not mention the exact aetiologies (Krause and Backonja, 2003). It is thus difficult to determine the potential specificity of pain associated with a nerve injury on the basis of these studies.

The French Neuropathic Pain Group consisting of a panel of experts addressed this question in a prospective study designed to compare patients with chronic pain associated with neurological (peripheral or central) or somatic tissue injuries. Analysis of the similarities and differences between these two categories of patients might allow identification of symptoms or association of symptoms preferentially or selectively associated with nervous lesions. This comparison was based on a new questionnaire, which includes both pain descriptors and items related to bedside examination. This questionnaire was called DN4, which stands for 'douleur neuropathique 4 questions' (i.e. neuropathic pain four questions in French). The psychometric properties of this instrument were specifically analyzed since it could represent a useful tool for the diagnosis of neuropathic pain.

2. Methods

The study was approved by the Local Ethical Committee and the patients gave informed written consent.

2.1. Patients

The inclusion criteria were: men or women with pain of at least moderate severity ($\geq$40 on a 100 mm Visual Analog Scale), a duration of at least 3 months and which could be attributed to a non-malignant nervous (peripheral or central) or somatic lesion. Diagnoses of nervous or somatic lesion were based on medical history, physical examination, electromyography and/or imaging when indicated.

The exclusion criteria were: painful syndromes of unknown origin or associated with diffuse pains (e.g. fibromyalgia), pains presumably of mixed origin (e.g. lumbar or cervical radiculopathies and cancer pains), CRPS type I, headaches, visceral pains, severe depression, chronic alcoholism or substance abuse, or any reason preventing an accurate understanding of the questionnaire.

2.2. Development of the questionnaire

On the basis of clinical experience and analysis of the literature, the Fench Neuropathic Pain Group compiled an initial list of symptoms and signs associated with neuropathic pains. The questionnaire derived from this list, called DN4, included a series of four questions consisting of both sensory descriptors and signs related to bedside sensory examination. This provisional questionnaire was not intended to be exhaustive and was deliberately restricted to a minimum of simple and presumably discriminant items requiring yes or no responses. Two questions (I and II) were based on the interview of the patient and two questions (III and IV) were based on a standardized clinical examination.

Question I included 5 items related to the description of pain:

'Does your pain have one or more of the following characteristics? ——' 1—burning ('brûlure'), 2—squeezing ('sensation de serrement'), 3—painful cold ('sensation de froid douloureux'), 4—'electric shock' ('décharges électriques'), 5—'lancinating' ('élancements').

Question II included 4 items related to the association of paresthesia/dysesthesia within the painful area:

'Is the pain associated with one or more of the following symptoms in the same area? ——' 6—pins and needles ('picotements'), 7—tingling, ('fourmillements'), 8—numbness ('engourdissement'), 9—itching ('démangeaisons').

Question III included 4 items related to sensory deficits:

'Is the pain located in an area where the physical examination may reveal one or more of the following characteristics? ——' 10—touch hypoesthesia ('hypoesthésie au tact'), 11—pricking hypoesthesia ('hypoesthésie à la piqûre'), 12—heat hypoesthesia ('hypoesthésie à la chaleur'), 13—cold hypoesthesia ('hypoesthésie au froid').

Question IV included 4 items related to evoked pains:

'In the painful area, can the pain be caused or increased by any of the following? ——' 14—brushing ('frottement'), 15—pressure ('pression'), 16—contact with cold ('contact avec le froid'), 17—contact with heat ('contact avec le chaud').

Examination of sensitivity to touch and pricking was made by means of a soft brush and a Von Frey hair (no. 13, Somedic),

respectively. Thermal (heat and cold) sensory examination was performed by means of two thermo-rollers (Somedic) set at constant temperatures of 40 and 25 °C.

The soft brush (three movements) was also used to evaluate tactile (i.e. dynamic mechanical) allodynia. Pressure allodynia (i.e. static mechanical allodynia) was tested by blunt pressure with a finger at a pressure that does not provoke pain in a normal area.

2.3. Study design

The study was carried out in 14 French multidisciplinary pain centers. Each patient was seen by two investigators in each center within an interval of 3 days. No treatment was initiated between the two visits. All the investigators were physicians experienced in pain medicine and trained in neurology.

The first investigator proposed a diagnosis of neuropathic or non-neuropathic pain on the basis of interview and examination performed according to his/her usual practice. Then, in order to fill out the questionnaire described above, the investigator had to perform a standardized interview by reading out each item of question I and II and a standardized examination. The patient was then referred to the second investigator, blinded to the results of the first visit, who proceeded similarly. The second investigator proposed a diagnosis of neuropathic or non-neuropathic pain on the basis of interview and examination performed according to his/her usual practice and, secondarily, administered the standardized questionnaire as described above. During each visit, both the patient and investigator rated the quality of each item ('bad', 'moderate', 'good') for clarity in wording, understanding and clinical relevance. After the second visit a treatment was proposed to the patient according to the usual practice of each center.

2.4. Statistical analysis and assessment of the psychometric properties of DN4

Only the data from patients whose diagnosis was similar between the two investigators were analyzed. For all statistical analyses the type 1 error has been set at 5%. The quantitative variables were described using mean, standard deviation (SD) and range; qualitative variables were described using frequency and percentages. For each item, the proportion of positive responses was compared between the two populations (neuropathic pain (NP) and non-neuropathic pain (NNP)) using a χ^2 test.

The analysis of the psychometric properties of the DN4 questionnaire included: face validity, that is to say clarity of wording, presentation and clinical relevance of each item, evaluated on the basis of the qualitative rating made by both the patients and investigators. Inter-rater reliability (i.e. agreement between the two experts) was evaluated for each item by measuring the Cohen Kappa coefficient. A factor analysis, using a principal component analysis with varimax rotation on tetrachoric coefficients, was performed to identify related items. Then, logistic regression modelling and estimation of the odd-ratio (with 95% confidence interval) of each item was performed to identify the most discriminant items and combinations of items for the diagnosis of NP. In this procedure, the diagnosis of NP (or NNP) made by the investigators was considered as the gold standard. A score of 1 was given for each positive response and a score of 0 for each negative response and the global score was defined as the sum of the responses to all the items. Sensitivity, specificity percentage of well classified observations and Youden index (i.e. sensitivity + specificity − 1) (Taube, 1986), were calculated for different values of the global score of the questionnaire. The corresponding ROC (receiver operating characteristics) curves were plotted and AUC calculated according to the trapezoid method.

3. Results

3.1. Description of the patients

A total of 167 patients were included between March 2002 and March 2003 and completed the two visits. The data from 7 patients were not analyzed because of discordance in the diagnosis made by the two investigators. Clinical and demographic details of the 160 patients included in the analysis, 71 (44.4%) with non-neuropathic pains (NNP) and 89 (55.6%) with neuropathic pain (NP), are presented in Table 1. Both groups were similar in terms of age, mean pain intensity and duration. NP included both peripheral ($n=69$) and central ($n=20$) lesions and NNP were represented by osteoarthritis, inflammatory arthropathies and mechanical low back pain (see Table 2).

3.2. Comparison of the clinical features of NP and NNP

As detailed in Table 3, the responses to the questions based on the interview (i.e. questions I and II including items 1–9), showed significant differences in the prevalence of sensory descriptors between NP and NNP. Most of the descriptors had a high prevalence (i.e. >65%) and were more prevalent in NP than in NNP (except items 2—'squeezing' and 5—'lancinating').

Comparison of the responses to questions III and IV (including items 10–17) related to clinical examination are presented in Table 4. Not surprisingly, sensory deficits were much more frequent in NP than in NNP patients. Evoked pains (i.e. cold, heat and brush-evoked allodynia) were also more frequent in NP, but the prevalence of pressure allodynia was not different between the two groups. The general prevalence of the items related to evoked pains (i.e. 20–45%) was lower than that of the items related to the interview.

Table 1
Demographic data

	Non-neuropathic pain ($n=71$)	Neuropathic pain ($n=89$)	Total ($n=160$)
Age (years) (mean ± SD)	57 ± 17	56 ± 14	56 ± 16
Male	17	40	57
Female	54	49	103
Pain intensity (mean VAS score ± SD)	67 ± 15	68 ± 16	67 ± 15
Pain duration (months) (mean ± SD)	70.1 ± 91.8	60 ± 73.9	64.5 ± 82.2

Table 2
Aetiology of pain in the two groups of patients

Aetiology of neuropathic pain ($n=89$)	*n* (%)
Nerve trauma	44 (49.5)
Postherpetic neuralgia	12 (13.5)
Polyneuropathies	12 (13.5)
Begnin tumor	1 (1.1)
Spinal cord injury	5 (5.6)
Post-stroke pain	11 (12.4)
Multiple sclerosis	4 (4.5)
Aetiology of non-neuropathic pain ($n=71$)	
Osteoarthritis	40 (56.3)
Inflammatory arthropathies	23 (32.4)
Mechanical low back pain	8 (11.3)

The prevalence of sensory descriptors and items related to evoked pains was similar between men and women. The frequency of the items was also similar between patients presenting with peripheral or central lesions, except the item related to pain increased by pressure which was more frequent in patient with a peripheral lesion (i.e. 54% vs 31%, $P<0.01$).

3.3. Analysis of the psychometric properties of the questionnaire

3.3.1. Face validity

The wording and clinical relevance of individual items and of the whole questionnaire were considered as good by a large majority of patients and investigators (i.e. 90–95%).

3.3.2. Inter-rater reliability

The crude agreement for the response to each item between the two visits was very high (i.e. 86–98%), although it was slightly lower for the items related to examination (i.e. 86–90%). The inter-rater reliability was further confirmed by calculation of the Cohen Kappa coefficient for each item (see Table 5). Kappa values were between 0.70 and 0.96, except for item 16—'pain increased by contact with cold' (Kappa=0.66).

Table 3
Comparison of the frequency of sensory descriptors between NP and NNP

	Non-neuropathic pain *n* (%)	Neuropathic pain *n* (%)	Total *n* (%)	*P* value
Burning	21 (30.4)	56 (68.3)	77 (51.0)	<0.001
Squeezing	26 (37.7)	40 (48.8)	66 (43.7)	0.171
Painful cold	7 (10.1)	21 (25.6)	28 (18.5)	0.015
Electric shocks	12 (17.4)	53 (64.6)	65 (43)	<0.001
Lancinating	45 (65.2)	62 (75.6)	107 (70.9)	0.162
Tingling	11 (15.9)	49 (59.8)	60 (39.7)	<0.001
Pins and needles	12 (17.4)	54 (65.9)	66 (43.7)	<0.001
Itching	4 (5.8)	24 (29.3)	28 (18.5)	<0.001
Numbness	21 (30.4)	54 (65.9)	75 (49.7)	<0.001

Table 4
Comparison of the frequency of sensory dysfunction between NP and NNP

	Non-neuropathic pain *n* (%)	Neuropathic pain *n* (%)	Total *n* (%)	*P* value
Touch hypoaesthesia	4 (5.8)	53 (64.6)	57 (37.7)	<0.001
Prick hypoaesthesia	7 (10.1)	57 (69.5)	64 (42.4)	<0.001
Heat hypoaesthesia	4 (5.8)	58 (70.7)	62 (41.1)	<0.001
Cold hypoaesthesia	3 (4.3)	55 (67.1)	58 (38.4)	<0.001
Pain increased by brushing	3 (4.3)	34 (41.5)	37 (24.5)	<0.001
Pain increased by pressure	31 (44.9)	38 (46.3)	69 (45.7)	0.862
Pain increased by contact with cold	3 (4.3)	23 (28)	26 (17.2)	<0.001
Pain increased by contact with hot	3 (4.3)	17 (20.7)	20 (13.2)	0.003

3.3.3. Factor analysis

The factor analysis identified a 9-factor solution (see Table 6). The factor 1 included the 4 items (i.e. items 10–13) related to hypoesthesia, indicating that these items were inter-related. This was confirmed by analysis of the intercorrelation matrix which showed very high correlation coefficients (i.e. between 0.90 and 0.98) between these items. Factor 2 included the items related to evoked pains (except item 15—'pain increased by pressure'), whose inter-relation coefficients were also high. All the other factors included only one item, except factor 6 (including items 6—'tingling' and 7—'pins and needles').

3.3.4. Discriminant properties of the items and cut-off diagnostic value of the questionnaire

Logistic regression was performed to analyze the discriminant properties of the items for the diagnosis of neuropathic pain. Seven items were not included in this analysis. Three items (i.e. items 2—'squeezing', item 5—'lancinating' and item 15—'pain evoked or increased by pressure') were excluded because their prevalence was similar in NP and NNP (see Tables 3 and 4). Four items were excluded (i.e. item 12—'hypoesthesia to heat', Item 13—'hypoesthesia to cold', item 16—'pain increased by

Table 5
Analysis of the inter-rater reliability of each item with the Cohen Kappa coefficient

Sensory descriptors	Kappa	Sensory dysfunction	Kappa
Burning	0.96	Touch hypoaesthesia	0.78
Squeezing	0.83	Prick hypoaesthesia	0.76
Painful cold	0.86	Heat hypoaesthesia	0.82
Electric shocks	0.85	Cold hypoaesthesia	0.80
Lancinating	0.74	Pain increased by brushing	0.71
Tingling	0.70	Pain increased by pressure	0.71
Pins and needles	0.84	Pain increased by contact with cold	0.66
Itching	0.87	Pain increased by contact with hot	0.74
Numbness	0.72		

Table 6
Fator analysis with loading of the items on the 9-factor solution

	Factors								
	1	2	3	4	5	6	7	8	9
Burning	0.24	0.13	0.01	0.16	−0.07	0.14	0.07	0.06	**0.92**
Squeezing	0.14	0.07	0.02	0.00	0.14	0.04	0.01	**0.96**	0.06
Painful cold	0.16	0.09	**0.95**	0.12	0.02	0.04	0.21	−0.02	0.02
Electric shocks	0.49	0.34	0.09	0.20	0.24	0.09	0.00	−0.23	0.26
Lancinating	0.12	0.20	0.04	0.01	**0.95**	0.10	0.03	0.16	−0.06
Tingling	0.39	0.17	0.19	0.50	0.12	**0.64**	−0.22	−0.08	0.08
Pins and needles	0.40	0.25	0.05	0.29	0.12	**0.73**	0.09	0.14	0.27
Itching	0.24	0.10	0.07	**0.91**	0.00	0.20	0.02	0.01	0.16
Numbness	0.48	0.25	0.55	−0.11	0.15	0.37	−0.19	0.22	−0.07
Touch hypoaesthesia	**0.93**	0.07	−0.03	0.10	0.17	0.22	0.03	0.04	0.16
Prick hypoaesthesia	**0.91**	0.11	0.09	0.22	0.17	0.10	−0.04	0.10	0.10
Heat hypoaesthesia	**0.93**	0.19	0.15	0.08	0.02	0.13	−0.05	0.02	0.08
Cold hypoaesthesia	**0.94**	0.14	0.16	0.10	−0.13	0.10	−0.06	0.11	0.08
Pain increased by brushing	0.35	**0.79**	−0.11	0.06	−0.19	0.19	0.39	0.08	0.10
Pain increased by pressure	−0.11	0.24	0.18	−0.01	0.04	−0.04	**0.95**	0.01	0.06
Pain increased by contact with cold	0.20	**0.92**	0.12	0.02	0.19	0.10	0.12	−0.05	0.09
Pain increased by contact with hot	0.02	**0.79**	0.22	0.20	0.33	0.07	0.00	0.17	0.06

cold', item 17—'pain increased by heat') because they were highly inter related with other items (see Section 3.3.3). Another reason to exclude these items was that the assessment of thermal sensitivity was considered less practical due to the use of special equipment.

The cut-off diagnositic value was determined on the basis of the percent of neuropathic pain (NP) patients correctly identified, sensitivity, specificity and Youden index, corresponding to the different total scores (i.e. sum of the positive items). A cut-off score of 4 resulted in the highest percent of correctly identified patients (86.0%), sensitivity (82.9%) and specificity (89.9%) of this 10-item questionnaire including both sensory descriptors and sensory examination (see Table 5). The ROC curve plotted for the total score (AUC = 0.92) is presented in Fig. 1.

The same procedure was used to analyze the diagnostic properties of the 7-items not related to examination (see Table 6). In this 7-item format of the questionnaire, called DN4-interview, a cut-off score of 3 resulted in the highest % of correctly identified patients (i.e. 79.5%), sensitivity (78.0%) and specificity (81.2%). The ROC curve plotted for DN4-interview total score (AUC = 0.87) is presented in Fig. 2.

3.3.5. Linguistic validation

The French version of the 10-item questionnaire DN4 is presented in Appendix A and an English translation is proposed in Appendix B. This translation was performed using the iterative forward–backward translation sequence but has not yet been formally validated with English-speaking patients (Tables 7 and 8).

4. Discussion

The systematic comparison of patients with neuropathic or non-neuropathic pains showed that several symptoms (i.e. pain descriptors and paresthesia/dysesthesia) and signs (i.e. evoked pains and sensory deficits) are significantly more frequent in patients with a definite neurological lesion. Although none of these symptoms or signs were pathognomonic or specific, the present data confirm that pains associated with a nerve injury have special qualities. In addition, we demonstrated that a relatively small number of items, including or not the signs evidenced by sensory examination, might be sufficient to discriminate NP and NNP.

The issues of neuropathic pain definition and diagnosis have been highly debated in the last few years (Backonja, 2003;

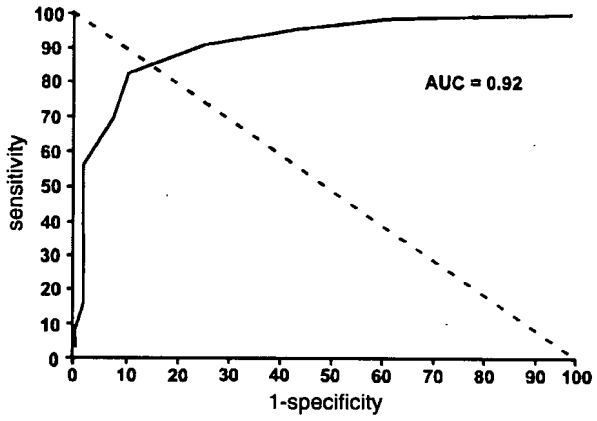

Fig. 1. ROC curve and AUC for the total score (i.e. sum of the 10 items) of the DN4 questionnaire.

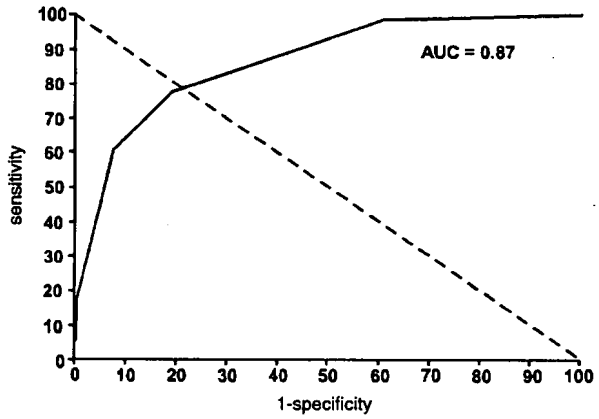

Fig. 2. ROC curve and AUC for the total score (i.e. sum of the 7 items) of the DN4-interview.

Bennett, 2003; Hansson, 2003; Max, 2002). Most of the discussions were based on theoretical arguments, within the more general framework regarding the classification of pain syndromes and the relevance or feasibility of a mechanisms-based classification (Hansson, 2003; Jensen and Baron, 2003; Max, 2000; Woolf and Max, 2001; Woolf et al., 1998). The lack of standardization in the approach of neuropathic pain, even among specialists, has probably represented a major limiting factor in clinical studies. Traditionally, the diagnosis of neuropathic pain has relied largely on sensory examination rather than on pain descriptors, which were not thought to be sufficient for the diagnosis of neuropathic pain (e.g. Baron, 2000; Dworkin, 2002; Hansson, 2002; Jensen et al., 2001; Rasmussen et al., 2004). The present results suggest that some pain symptoms are expressed preferentially in neuropathic pain patients and have a clear discriminant value. In particular, our results indicate that the association of painful symptoms and paresthesia/dysesthesia has a high specificity and diagnostic value. Thus, although it is determinant for the diagnosis of a nervous lesion, the clinical examination might not be mandatory for the diagnosis of neuropathic pain per se (Attal and Bouhassira, submitted; Bouhassira and Attal, in press).

Table 7
Sensitivity, specificity and Youden index, corresponding to the total scores (i.e. sum of items) of the 10-item version of the questionnaire DN4 including both sensory descriptors and sensory examination

Total score (sum of positive items)	Sensitivity	Specificity	Youden index
0	100	0	0
1	98.8	37.7	0.36
2	95.1	59.4	0.55
3	90.3	76.8	0.67
4	82.9	89.9	0.73
5	69.5	92.7	0.62
6	56.1	98.5	0.55
7	35.4	98.5	0.34
8	15.8	98.6	0.14
9	8.5	100	0.09
10	2.4	100	0.02

A cut-off score of four resulted in the highest % of correctly identified patients, sensitivity and specificity.

Table 8
Sensitivity, specificity and Youden index, corresponding to the total scores (i.e. sum of items) of the 7-item version of the questionnaire DN4 including only the sensory descriptors

Total score (sum of positive items)	Sensitivity	Specificity	Youden index
0	100	0	0
1	98.8	39.1	0.38
2	86.6	62.3	0.49
3	78.0	81.2	0.59
4	61.0	92.7	0.54
5	32.9	97.1	0.30
6	17.0	100	0.17
7	4.9	100	0.05

A cut-off score of three resulted in the highest % of correctly identified patients, sensitivity and specificity.

In the present study, the initial diagnosis of neuropathic or non-neuropathic pain was based on interview and examination performed according to the usual practice of the investigators. Thus, although the diagnosis was not based on the DN4 questionnaire, some of the questions used by the investigators in their initial interview may have been similar, at least to some extent, to those included in the standardized questionnaire administered secondarily. Such an apparently circular procedure represents a limitation, but is unavoidable in this type of study in the absence of true 'gold standard'. The fact that each patient was seen independently by two investigators and that a large number of centers and investigators participated in the study tend to limit the risk of systematic bias and made unlikely, for instance, a bias due to some 'preconceptions' about neuropathic pain.

The DN4 questionnaire developed and validated in the present study, is a clinician-administered questionnaire which has been deliberately reduced to a minimum number of items and simplified in its scoring. A score of 1 is given to each positive item and a score of 0 to each negative item. The total score is calculated as the sum of the 10 items and the cut-off value for the diagnosis of neuropathic pain is a total score of 4/10. Thus, this new diagnostic tool could be easily used by pain specialists or non-specialists in daily clinical practice as a screening tool to better detect neuropathic pain. In addition, the good discriminant properties of the 7 items based on the interview alone (i.e. DN4-interview) suggest that this questionnaire could be used in a very large range of clinical studies including, for example, telephonic surveys and make it suitable for epidemiological studies. For this purpose, the validity of the 7 items as a self-questionnaire is now being investigated. The DN4 questionnaire has significant differences with the two recently developed diagnostic tools, namely the LANSS Pain Scale (Bennett, 2001) and the Neuropathic Pain Questionnaire (NPQ) (Krause and Backonja, 2003).

For example, in the LANSS pain scale, the 5 questions based on the interview are 'open' questions since they do not include single items but associations of several descriptors. In addition, each of these questions has a different 'weight' in the total score. The question related to changes in the color of the skin in the painful area has the highest weight for the diagnosis of neuropathic pain. This might reflect the over representation of CRPS in the neuropathic pain group included in the validation study. The present data indicate that such 'autonomic symptoms' are not essential for the diagnosis of pain associated with a definite neurological lesion. Indeed, the specificity and sensitivity of the items included in the DN4 questionnaire appeared higher than those of the LANSS pain scale. By contrast with DN4 and the LANSS pain scale, the NPQ (Krause and Backonja, 2003) is a self-questionnaire and therefore does not include sensory examination. The NPQ includes items related to the affective dimension of pain, whose specificity is generally considered as poor (e.g. Boureau et al., 1990), or even less specific items such as the changes of pain related to meteorological factors. The weak discriminant properties of these items might explain the relatively modest sensitivity and specificity of the NPQ as a diagnostic tool (i.e. 66 and 74%, respectively). The present data indicate that a questionnaire based exclusively on sensory descriptors has a higher specificity, but future comparative studies should aim to further define the advantages and limitations of these different diagnostic tools. Furthermore, DN4 is complementary to the Neuropathic Pain Scale (Galer and Jensen, 1997) or the Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al., 2004) developed recently for the evaluation of the different symptoms and dimensions of neuropathic pains and particularly suitable to assess treatment outcome. Indeed, the diagnosis and the evaluation are two different processes which do not depend necessarily on the same items.

Despite the differences between the DN4, NPQ and LANSS pain scale mentioned above, it appears that several items are common to these three questionnaires (e.g. burning, electric shocks, tingling). These items, which were also the most discriminant of the McGill Pain Questionnaire (Boureau et al., 1990), could probably constitute a basis for a new consensual and operational definition of neuropathic pain.

In conclusion, the present results indicate that a simple combination of symptoms can lead to discrimination between pains associated with an injury to the nervous system and those related to other somatic lesions, which may reflect differences in their underlying pathophysiological mechanisms. Such results are important in the absence of validated criteria or even consensus among specialists regarding the diagnosis of neuropathic pain, including the 'pure' neuropathic conditions. However, before this questionnaire can be generalized to all types of neuropathic pains, a similar comparative approach should be used to determine whether the neuropathic pain component present in more complex pain conditions presumably of mixed origin (e.g. lumboradicular pain) includes similar symptoms. It would also be of interest to determine whether pain syndromes due to a putative dysfunction of the nervous system (e.g. CRPS type I, fibromyalgia) are similar or different to pains associated with a definite injury to the nervous system. Eventually, such a clinical approach should allow to propose positive clinical diagnostic criteria of neuropathic pain. This would be of major interest not only in daily practive but also in the clinical research setting, most notably for selecting more homogeneous groups of patients in future therapeutical trials.

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Appendix A

Questionnaire DN4

Répondez aux 4 questions ci-dessous en cochant une seule case pour chaque item.

INTERROGATOIRE DU PATIENT

Question 1: La douleur présente-t-elle une ou plusieurs des caractéristiques suivantes?

	oui	non
1 - **Brûlure**	☐	☐
2 - **Sensation de froid douloureux**	☐	☐
3 - **Décharges électriques**	☐	☐

Question 2: La douleur est-elle associée dans la même région à un ou plusieurs des symptômes suitvants?

	oui	non
4 - **Fourmillements**	☐	☐
5 - **Picotements**	☐	☐
6 - **Engourdissement**	☐	☐
7 - **Démangeaisons**	☐	☐

EXAMEN DU PATIENT

Question 3: La douleur est-elle localisée dans un territoire ou l'examen met en évidence?

	oui	non
8 - **Hypoesthésie au tact**	☐	☐
9 - **Hypoesthésie à la piqûre**	☐	☐

Question 4: La douleur est-elle provoquée ou augmentée par:

	oui	non
10 - **Le frottement**	☐	☐

Appendix B

DN4 Questionnaire

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	yes	no
1 - **Burning**	☐	☐
2 - **Painful cold**	☐	☐
3 - **Electric Shocks**	☐	☐

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	yes	no
4 - **Tingling**	☐	☐
5 - **Pins and Needles**	☐	☐
6 - **Numbness**	☐	☐
7 - **Itching**	☐	☐

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	yes	no
8 - **Hypoesthesia to touch**	☐	☐
9 - **Hypoesthesia to prick**	☐	☐

Question 4: In the painful area, can the pain be caused or increased by:

	yes	no
10 - **Brushing**	☐	☐

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